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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,986	KONDOH, GEN	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/28/05;8/8/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. In the preliminary amendment filed April 28, 2005, claims 5 has been amended, and new claims 11-19 have been added, therefore, claims 1-19 are pending and examined.

Informalities

The disclosure is objected to because of the following informalities:

2. The specification recites the amino acid sequence of His-Glu-Met-Gly or His-Glu-Met-Gly-His (e.g., at page 4, lines 6 and 8) without providing the sequence identifier "SEQ ID NO:". Applicant must comply with the requirements of sequence rules (37 CFR 1.821-1.825) to file a Sequence Listing (i.e., a paper copy and a computer readable form) containing all the sequences. Appropriate correction is required.

3. The specification indicates the ACE shedding activity for CD59 was ACE dose-dependent (shown in Fig. 11) and was inhibited by captopril (shown in Fig. 12) at page 22, lines 25-26. However, it is Fig. 12 that indicates ACE dose-dependent effect, and Fig. 13 shows the inhibition by captopril. Appropriate correction is required.

Claim Objections

4. Claims 6, 7, 9, 10 and 14-19 are objected to because the claims recite the amino acid sequence of His-Glu-Met-Gly or His-Glu-Met-Gly-His without providing the sequence identifier "SEQ ID NO:". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-7 and 11-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising a mutant of an angiotensin-converting enzyme (ACE) and a pharmaceutically acceptable carrier, wherein the mutant has GPI-anchored protein releasing activity and is the ACE consisting of a substitution of Glu by Asp in the zinc binding sequence of His-Glu-Met-Gly-His; and an ACE-containing drug having the activity of suppressing accumulation of β-amyloid protein as indicated in the prior art, does not reasonably provide enablement for an angiotensin-converting enzyme (ACE) containing medicine, of which action mechanism is release of GPI-anchored protein from the cell surface, where the medicine can be used for preventing and curing prion-related diseases, bacterial infectious diseases, or male infertility due to sperm abnormality, and where the ACE can be a mutant having GPI-anchored protein releasing activity but its peptidase activity being inactivated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-7 and 11-19 encompass an angiotensin-converting enzyme (ACE) containing medicine, of which action mechanism is release of GPI-anchored protein from the cell surface, where the medicine can be used for preventing and curing prion-related diseases, bacterial infectious diseases, or male infertility due to sperm abnormality, and where the ACE can be a mutant having GPI-anchored protein releasing activity but its peptidase activity being inactivated. The specification, however, only discloses cursory conclusions without data supporting the findings, which state that ACE, either wild type or a mutant, has GPI-anchored protein releasing activity, the GPI-anchored proteins are the proteins that bound to cell

membrane via GPI-anchor, such as normal and pathogenic prion protein and CD14 (the receptor for LPS), and cleaving GPI-anchor from GPI-anchored proteins can inactivate their harmful functions (pages 3-4). There are no indicia that the present application enables the full scope of the claims in view of an ACE having GPI-anchored protein releasing activity as a medicine as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to enable the full scope of the claims. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the absence or presence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the ACE-containing medicine having GPI-anchored protein releasing activity, and the use of these ACE variants in the preventing and curing prion-related diseases, bacterial infectious diseases, or male infertility due to sperm abnormality, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

The specification discloses that identification of GPI-anchored protein releasing factor is an ACE (section 2.2); ACE (either wild type or E414D mutant) can release certain GPI-anchored proteins from cell surface (section 2.3); GPI-anchored protein is cleaved by ACE (section 2.4);

and the GPI-anchored protein releasing activity of ACE is related to the sperm binding activity to eggs (section 2.5). However, there are no working examples indicating the use of an ACE having GPI-anchored protein releasing activity in the treating, preventing and curing prion-related diseases, bacterial infectious diseases, or male infertility due to sperm abnormality.

(3). The state of the prior art and relative skill of those in the art:

The related art (e.g., Ko *et al.*, JP 2001-316287) discloses a drug, which contains an angiotensin-converting enzyme (ACE) having the activity of suppressing accumulation of β-amyloid protein, is used to treat Alzheimer's disease. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide teachings on the use of various ACEs having GPI-anchored protein releasing activity in the treating, preventing and curing prion-related diseases, bacterial infectious diseases, or male infertility due to sperm abnormality to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass an angiotensin-converting enzyme (ACE) containing medicine, of which action mechanism is release of GPI-anchored protein from the cell surface, however, the use of the ACE variants in the treatment of diseases are not adequately described in the specification, the invention is unpredictable regarding the structures of ACE that are effective in treating, preventing and curing prion-related diseases, bacterial infectious diseases, or male infertility.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to an angiotensin-converting enzyme (ACE) containing medicine, of which action mechanism is release of GPI-anchored protein from the cell surface. While the specification discloses ACE (either wild type or E414D mutant) can release certain GPI-anchored proteins from cell surface (section 2.3); GPI-anchored protein is cleaved by ACE (section 2.4); and the GPI-anchored protein releasing activity of ACE is related to the sperm binding activity to eggs (section 2.5), the specification does not describe the use of various ACEs having GPI-anchored protein releasing activity in the treating, preventing and curing prion-related diseases, bacterial infectious diseases, or male infertility, nor indicates how to extrapolate the in vitro effect to in vivo treatment. Furthermore, there are no working examples indicating the use of ACEs having GPI-anchored protein releasing activity in the treatment of diseases and their effects in the treatment. Furthermore, the specification does not show the ACEs can prevent and cure the diseases; and how the diseases can be monitored if the disease never occurs (i.e., prevention). Since the specification does not provide sufficient teachings on the use of various ACEs having GPI-anchored protein releasing activity in the treatment of the diseases, it is necessary to carry out undue experimentation to identify the ACEs that have GPI-anchored protein releasing activity and are effective for in vivo treatment.

(6). Nature of the Invention

The scope of the claims encompasses an angiotensin-converting enzyme (ACE) containing medicine, of which action mechanism is release of GPI-anchored protein from the cell surface, but the specification does not provide sufficient teachings on the identities of ACES that are effective in the treatment of diseases. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broader than the enabling disclosure. The working examples do not demonstrate the claimed medicine, the structures of active ACE and their effects in the in vivo treatment are unpredictable, and the teachings in the specification are limited, therefore, it is necessary to carry out undue experimentation to identify the ACEs having GPI-anchored protein releasing activity that are active in the treatment of diseases.

6. Claims 1-7 and 11-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-7 and 11-19 are directed to an angiotensin-converting enzyme (ACE) containing medicine, of which action mechanism is release of GPI-anchored protein from the cell surface, where the medicine can be used for preventing and curing prion-related diseases, bacterial infectious diseases, or male infertility due to sperm abnormality, and where the ACE can be a mutant having GPI-anchored protein releasing activity but its peptidase activity being inactivated.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by

actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

While the specification discloses ACE, either wild type or a mutant (e.g., Glu→Asp in the Zn binding region of His-Glu-Met-Gly-His), has GPI-anchored protein releasing activity, the GPI-anchored proteins are the proteins that bound to cell membrane via GPI-anchor, such as normal and pathogenic prion protein and CD14 (the receptor for LPS), and cleaving GPI-anchor from GPI-anchored proteins can inactivate their harmful functions (pages 3-4), as well as the GPI activity of ACE is related to the sperm binding to eggs (Page 23, line 25-page 24, line 18), the specification does not describe the correlation between function and structure in the variants of ACE, nor discloses treating, preventing and curing prion-related diseases, bacterial infectious diseases, or male infertility with an ACE-containing medicine having GPI-anchored protein releasing activity. Furthermore, the specification does not describe the effect of ACE in the treatment of these diseases. Without guidance on structure to function/activity in the variants of ACE having GPI-anchored protein releasing activity, one skilled in the art would not know which ACE is functional, and which ACE can be used as a medicine for treating diseases. The lack of a structure to function/activity relationship of the ACE variants, and the lack of

representative species for the whole genus of ACE variants as medicine for the treatment of various diseases as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-7 and 11-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 1-7 and 11-19 are indefinite because of the use of the term "GPI", it is not clear what the term means. A fully spelled out word should be indicated in the first occurrence. Claims 2-7 and 11-19 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend.

9. Claims 2-4 and 11-19 are indefinite because claims 2-4 do not further limit the independent claim, claim 1. The term cited "for preventing and curing prion-related diseases", "for preventing and curing bacterial infectious diseases", or "for preventing and curing male infertility due to sperm abnormality" is an intended use, which does not further limit the angiotensin-converiting enzyme containing medicine. Claims 11-19 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-4 are rejected under 35 U.S.C. 102(a) as being anticipated by Ko *et al.* (JP 2001-316287, published on November 13, 2001, English abstract).

Ko *et al.* teach a drug, which contains an angiotensin-converting enzyme (ACE) having the activity of suppressing accumulation of β-amyloid protein as an active component, is used to treat Alzheimer's disease (see English abstract). Although the reference does not indicate ACE can release GPI-anchored protein from the cell surface, the ACE-containing drug taught by the reference is not different from the claimed ACE-containing medicine, which meets the criteria of claims 1-4. The term "for preventing and curing prion-related diseases", "for preventing and curing bacterial infectious diseases", or "for preventing and curing male infertility due to sperm abnormality" is an intended use, which does not have weight in a product claim.

11. Claims 8-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Wei *et al.* (J. Biol. Chem. 266, 9002-9008 (1991)).

Wei *et al.* teach angiotensin-converting enzyme (ACE) contains two zinc binding sites (HEMGH, residues 361-365 and 959-963), and mutations in two these two regions of ACE, e.g., ACE_{D362}, ACE_{D960}, $ACE_{K361,365}$, $ACE_{K959,963}$, $ACE_{D362,960}$ and $ACE_{K361,365,959,963}$ (Fig. 1), result in inactivation of the corresponding active site (pages 9003-9005; Tables I-III; claims 8-10).

12. Claims 8-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Jaspard *et al.* (J. Biol. Chem. 268, 9496-9503 (1993)).

Jaspard *et al.* teach angiotensin-converting enzyme (ACE) contains two zinc binding sites (HEMGH, residues 361-365 and 959-963), and mutations in two histidines of ACE, e.g., ACE K 361,365 and ACE K 959,963 (Fig. 1), result in inactivation of the corresponding active site (pages 9498-9499; Tables I-II; claims 8-9).

13. Claim 8 is rejected under 35 U.S.C. 102(b) as being anticipated by Sen *et al.* (J. Biol. Chem. 268, 25748-25754 (1993)).

Sen *et al.* teach mutations in two residues (Lys-154 and Tyr-236) of testicular angiotensin-converting enzyme, e.g., two single mutants, ACE_TK154E and ACE_TY236F, and one double mutant (i.e., Tyr→Phe and Lys→Glu), where the enzymatic properties of the two single mutants and the wild type enzyme are similar, however the double mutant has about 20-fold lower specific activity and a Km value 8-fold higher than that of the wild type protein (abstract; page 25748, right column, last paragraph; page 25762, left column; Table I; claim 8).

Conclusion

14. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Bragdon can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Primary Patent Examiner

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PRIMARY EXAMINER

CMK
September 24, 2007